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Native functionality in triple catalytic cross-coupling: sp^3 C–H bonds as latent nucleophiles

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The use of sp^3 C–H bonds—which are ubiquitous in organic molecules—as latent nucleophile equivalents for transition metal-catalyzed cross-coupling reactions has the potential to dramatically streamline synthetic efforts in organic chemistry while bypassing substrate activation steps. Through the combination of photoredox-mediated hydrogen atom transfer (HAT) and nickel catalysis, we have developed a highly selective and general C–H arylation protocol that activates a wide array of C–H bonds as native functional handles for cross-coupling. This mild approach takes advantage of a tunable HAT catalyst that exhibits predictable reactivity patterns based on enthalpic and bond polarity considerations to selectively functionalize α -amino and α -oxy sp^3 C–H bonds in both cyclic and acyclic systems.

Over the past fifty years, transition metal-catalyzed cross-coupling reactions have transformed the field of synthetic organic chemistry via the evolution of a wide variety of C–C and C–heteroatom bond-forming reactions (1, 2). During this time, the seminal studies of Negishi, Suzuki, Miyaura, Stille, Kumada, and Hiyama have inspired numerous protocols to construct carbon–carbon bonds using palladium, nickel, or iron catalysis. These strategies enable highly efficient and regioselective fragment couplings with high functional group tolerance, facilitating the application of modular building blocks in early- or late-stage synthetic efforts. Traditionally, cross-coupling methods have relied upon the use of organometallic nucleophiles such as aryl or vinyl boronic acids, zinc halides, stannanes, or Grignard reagents that undergo addition to a corresponding metal-activated aryl or vinyl halide.

An emerging strategy for C–C bond formation has been the application of native organic functionality as latent nucleophilic handles for transition metal-mediated cross-couplings. In this context, the use of olefin, methoxy, acetoxy, and carboxylic acid moieties as organometallic replacements has enabled a variety of carbon–carbon bond formation protocols using feedstock materials (3–8). However, without question the most common approach for transition metal-mediated native functionalization has been the use of C–H bonds—the most ubiquitous chemical bonds found in nature—as nucleophilic coupling partners. Among the well-established challenges with sp^3 C–H bond functionalization, regioselectivity is perhaps preeminent, given that organic molecules incorporate a diverse combination of methyl, methylene, and/or methine groups. Several elegant methodologies have navigated this question via the use of

directing groups to accomplish selective sp^3 C–H bond functionalization (9–13), or more recently by focusing upon the use of inductive effects to deactivate C–H bonds (14). Enzymes accomplish selective sp^3 C–H bond functionalization by taking advantage of the diverse electronic and enthalpic characteristics of carbon–hydrogen bonds found within complex organic molecules (15). Inspired by this biochemical blueprint, we speculated that a small-molecule catalyst platform could be developed that would differentiate between a diverse range of C–H groups using a combination of bond energies and polarization, thereby enabling a unique pathway toward native arylation or vinylation.

A fundamental mechanistic step in organic synthesis is the simultaneous movement of a proton and an electron—a process termed hydrogen atom transfer (HAT) (16, 17). HAT has long served as an effective way to access radical intermediates in organic chemistry; however, the capacity to regioselectively abstract hydrogens among a multitude of diverse C–H locations has been notoriously difficult to control. Recently, driven by developments in small-molecule catalyst design, general methods for C–H bond functionalization via HAT have begun to achieve levels of selectivity that were previously restricted to enzymatic systems (18, 19). In this context, our laboratory has demonstrated that photoredox-mediated HAT catalysis can exploit native sp^3 C–H bonds for a range of C–C bond constructions, such as Minisci reactions, conjugate additions, and radical–radical couplings (20–23). Nevertheless, a general strategy for functionalization of C–H bonds via HAT–transition metal cross-coupling has yet to be achieved (24, 25).

We recently questioned whether it would be possible to utilize a tertiary amine radical cation—generated via a pho-

toredox-mediated single electron transfer (SET) event (23, 26–28)—to accomplish H-atom abstraction from a diverse range of substrates (Fig. 1). Given the electrophilic nature of amine radical cations, we proposed that such a catalytic strategy might allow the selective abstraction of hydridic, electron-rich C–H bonds in the presence of electron-deficient and neutral C–H bonds, which are abundant throughout organic molecules. We envisioned that the exploitation of polarity effects in the abstraction event would impart a high degree of kinetic selectivity into an otherwise unselective HAT process (29). Thereafter, we assumed the resulting radical intermediate might readily intersect with a Ni-catalyzed coupling cycle, thereby enabling C–C bond formation with a range of aryl electrophiles.

A detailed description of our proposed mechanistic cycle for the sp^3 C–H cross-coupling via photoredox HAT–nickel catalysis is outlined in Fig. 2. Initial excitation of the iridium(III) photocatalyst $\text{Ir}[\text{dF}(\text{CF}_3)\text{ppy}]_2(\text{dtbbpy})\text{PF}_6$ [$\text{dF}(\text{CF}_3)\text{ppy}$ = 2-(2,4-difluorophenyl)-5-(trifluoromethyl)pyridine, dtbbpy = 4,4'-di-*tert*-butyl-2,2'-bipyridine] (**1**) would produce the long-lived photoexcited state **2** (τ = 2.3 μs) (30). The $^*\text{Ir}(\text{III})$ catalyst **2** is sufficiently oxidizing to undergo SET with a tertiary amine HAT catalyst (such as **3**), to generate Ir(II) **4** and amine radical cation **5** ($E_{1/2}^{\text{red}}$ [$^*\text{Ir}^{\text{III}}/\text{Ir}^{\text{II}}$] = +1.21 V vs. saturated calomel electrode (SCE) in CH_3CN , E_p [3-acetoxyquinuclidine] = +1.22 V vs. SCE in CH_3CN) (30). As a central design element, we postulated that amine radical cation **5** would be sufficiently electron-deficient to engender a kinetically selective HAT event at the most electron-rich site of C–H nucleophile substrate **6**, thereby exclusively delivering radical intermediate **7**. At the same time, we hypothesized that this abstraction event should also be thermodynamically favorable considering the significant difference in the bond dissociation enthalpies (BDEs) of hydridic α -amino C–H bonds (α -amino C–H = 89–94 kcal/mol) and the resultant N–H bond of quinuclidinium (H–N⁺ BDE [quinuclidine] = 100 kcal/mol) (31, 32). Concurrent with this photoredox cycle, we assumed that our active Ni(0) species **9**—generated in situ via two SET reductions of (4,7-dOMe-phen)Ni(II)Br₂ (4,7-dOMe-phen = 4,7-dimethoxy-1,10-phenanthroline) by the iridium photocatalyst ($E_{1/2}^{\text{red}}$ [$\text{Ir}^{\text{III}}/\text{Ir}^{\text{II}}$] = –1.37 V vs. SCE in CH_3CN , $E_{1/2}^{\text{red}}$ [$\text{Ni}^{\text{II}}/\text{Ni}^0$] = –1.2 V vs. SCE in DMF) (30, 33)—would undergo oxidative addition into the aryl halide electrophile **10**, forming the electrophilic Ni(II)-aryl intermediate **11**. This Ni(II) species would rapidly intercept radical **7** to generate a Ni(III)-aryl-alkyl complex **12**, which upon reductive elimination would forge the desired C–C bond to form Ni(I) complex **13** and benzylic amine **14**. Reduction of **13** by **4**, the Ir(II) state of the photocatalyst, would then reconstitute both Ni(0) catalyst **9** and Ir(III) catalyst **1**.

We began our investigations into the proposed photore-

dox-mediated HAT nickel cross-coupling by evaluating a broad range of photoredox catalysts, nickel–ligand systems, and quinuclidine analogs. Upon exposing *N*-Boc pyrrolidine and methyl 4-bromobenzoate to visible light (34 W blue LEDs) in the presence of iridium photocatalyst $\text{Ir}[\text{dF}(\text{CF}_3)\text{ppy}]_2(\text{dtbbpy})\text{PF}_6$, $\text{NiBr}_2 \cdot 3\text{H}_2\text{O}$, 4,7-dimethoxy-1,10-phenanthroline, and 3-acetoxyquinuclidine, we were pleased to observe 81% yield of the desired α -amino C–C coupled product. More importantly, this product was the only detectable regioisomer formed, indicating that quinuclidine HAT catalyst **3** was selective for the most hydridic C–H bond available. Notably, employing quinuclidine in lieu of 3-acetoxyquinuclidine resulted in diminished reactivity, indicating the necessity for an electron-withdrawing substituent. This substantial difference in reaction efficiency illustrates the capacity to tune the reactivity of the HAT catalyst via electronic modification of the substituent at the 3-position. It is important to note that under these reaction conditions, amine **3** serves as both the HAT catalyst and the base (34).

With the optimal conditions in hand, we next sought to examine the generality of this transformation by exploring the scope of the electrophilic aryl halide coupling partner. As outlined in Fig. 3, a wide variety of bromoarenes functioned efficiently in this HAT cross-coupling protocol. For example, electron-deficient aryl bromides containing ketones, trifluoromethyl groups, fluorines, sulfones, and esters were all effective arylating agents (**15–18**, 71–84% yield). Notably, 4-chlorobromobenzene gave chlorophenyl amine product **19** as the only observable arylation product in 70% yield, demonstrating that a high degree of chemoselectivity can be achieved in the oxidative addition step. The HAT arylation strategy is further effective for electron-neutral and electron-rich aryl bromides, as demonstrated by the installation of phenyl, tolyl, *t*-Bu-phenyl, and anisole groups (**20–23**, 64–79% yield). The presence of *ortho* methyl or fluorine substitution on the aryl halide was not problematic (**24** and **25**, 70% and 60% yield). With respect to heteroaromatic systems, pyridine rings were incorporated with good efficiency via the use of the corresponding heteroaryl bromide (**26**, 65% yield). We were satisfied to see that heteroaryl chlorides were also effective electrophiles in the transformation. For example, electron-deficient pyridines and pyrimidines deliver the benzylic amine products in good efficiency (**27–29**, 61–83% yield) (35). The collective one step synthesis of the aryl pyrrolidine products **14–29** from simple *N*-Boc pyrrolidine clearly demonstrates that synthetic streamlining can be accomplished using this HAT cross-coupling technology (36).

We next explored the diversity of amino- and oxy-bearing C–H nucleophiles that could be employed as substrates in this photoredox-mediated HAT nickel-catalyzed cross-

coupling. As demonstrated in Fig. 3, many α -amino methyl- and methylene-containing substrates can be selectively arylated. For example, differentially *N*-substituted pyrrolidine substrates are effective in the transformation, including those bearing *tert*-butoxycarbonyl (Boc), benzyloxycarbonyl (Cbz), pivalate (Piv), and *tert*-butylaminocarbonyl (Bac) groups (**14**, **30–32**, 51–81% yield). Notably, the arylation of *N*-Boc pyrrolidine can be achieved on gram-scale in a single batch, delivering 1.34 g of the 2-arylpiperidine product **14** (78% yield). Cyclic amines of various ring size are readily tolerated with azetidine, piperidine, and azepane undergoing selective C–H arylation (**33–35**, 42–69% yield). Remarkably, ring systems that incorporate inductively withdrawing alcohols and fluorine substituents at the β -amino position do not unduly retard the C–H abstraction step (**36** and **37**, 45% yield, >20:1 d.r. and 68% yield, 3:1 d.r.). Moreover, lactams and ureas proved effective latent nucleophiles for this coupling, with both *N*-Me and *N*-H substrates providing the corresponding arylated products in good yield (**38–42**, 62–84% yield).

The transformation is not restricted to cyclic substrates, as a range of acyclic amines have been efficiently functionalized using this HAT arylation protocol. For example, primary α -amino C–H bonds can be arylated using both *N*-Boc alkyl amines and ureas (**43–45**, 47–74% yield). *N*-Boc butylamine, possessing a free N–H bond, undergoes selective α -arylation in 58% yield (**46**), leaving this latent functional handle available for further derivatization without the need for protection or deprotection steps. For acyclic dialkyl amines containing methylene C–H bonds, we were delighted to see that *N*-Bac substituted amines delivered the α -arylated products in excellent yield (**47–49**, 66–82% yield) while the corresponding Boc systems provided diminished yet usable efficiencies (20–30% yield). We attribute this interesting reactivity difference to the diminished electron-withdrawing nature of the Bac group in comparison to Boc, resulting in an increased rate of hydrogen atom transfer to the electrophilic amine radical cation **5**.

When unsymmetrical amine substrates were exposed to this HAT protocol, some interesting regioselectivity patterns were discovered. For example, methyl C–H bonds undergo preferential coupling over methylene C–H bonds, as shown with *N*-Bac butylmethylamine (**48**, 78% yield, 4:1 r.r.). Furthermore, methyl and methylene C–H bonds react exclusively over methine C–H bonds, as demonstrated with *N*-Bac isopropylmethylamine and *N*-Boc 2-methylpyrrolidine, respectively (**49** and **50**, 82% and 62% yield, 1:1 d.r.). This strategy can also be applied to the HAT arylation of α -oxy C–H bonds. Tetrahydrofuran (THF) and oxetane both undergo α -oxy arylation in good efficiency (**51** and **52**, 76% and 53% yield). Finally, we have been able to demonstrate that this C–H arylation protocol is effective for benzylic sys-

tems as *para*-xylene is arylated in 54% yield (**53**). Indeed, we expect that application of this strategy to a broad range of α -oxy, α -amino, and benzylic C–H-bearing substrates will demonstrate the general utility of this selective C–H arylation protocol.

Finally, we recognized that the capacity to control the regioselectivity of the outlined HAT abstraction along with the opportunity to utilize C–H bonds as latent nucleophiles brings forward the possibility of enabling multiple native functionalizations to be conducted in sequence—a strategy that should allow the rapid construction of molecular complexity from a large variety of readily available organic feedstock chemicals. As one example, we postulated that *N*-Boc proline methyl ester (**54**) might be differentially arylated via (i) the photoredox-mediated HAT method presented in this work, followed by (ii) a photoredox-mediated Ni(II) decarboxylative arylation. As shown in Fig. 4, *N*-Boc proline methyl ester underwent selective arylation at the 5-methylene position using the HAT cross-coupling strategy disclosed herein (66% yield, 4:1 d.r.). The observed regioselectivity is usefully complementary to that which would be expected using established methods for transition metal-catalyzed cross-coupling. Whereas many current strategies utilize basic conditions to selectively functionalize acidic hydrogens (as in enolate arylations), our developed HAT protocol targets hydridic hydrogen atoms, thereby providing access to fundamentally distinct product classes. Following the successful execution of the outlined C–H arylation, the corresponding amino acid product **55** successfully underwent decarboxylative coupling with 2-fluoro-4-bromopyridine at the 2-position delivering the 2,5-diarylated pyrrolidine adduct in excellent yield (**56**, 73% yield, 4:1 d.r.). We have also been able to demonstrate a HAT arylation followed by a nickel-catalyzed C–O coupling (**37**). *N*-Boc 3-hydroxyazetidine can be selectively arylated at the 2-position in 45% yield (**36**, Fig. 3), leaving the alcohol untouched. The free alcohol can then be subsequently arylated with 4-bromo-2-methylpyridine to deliver the aryl ether product in 77% yield (see Supplementary Material).

This HAT strategy represents a powerful demonstration of the versatility of using sp^3 C–H bonds as organometallic nucleophile equivalents and will likely find application in the realm of late-stage functionalization. We believe that this protocol will gain widespread use within the synthetic community as a complement to existing cross-coupling technologies.

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SUPPLEMENTARY MATERIALS

www.sciencemag.org/cgi/content/full/science.aaf6635/DC1

Tables S1 and S2

NMR Spectra

References (38–50)

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Traditional Cross-Coupling Regioselectivity Controlled by Nucleophile Pre-Activation

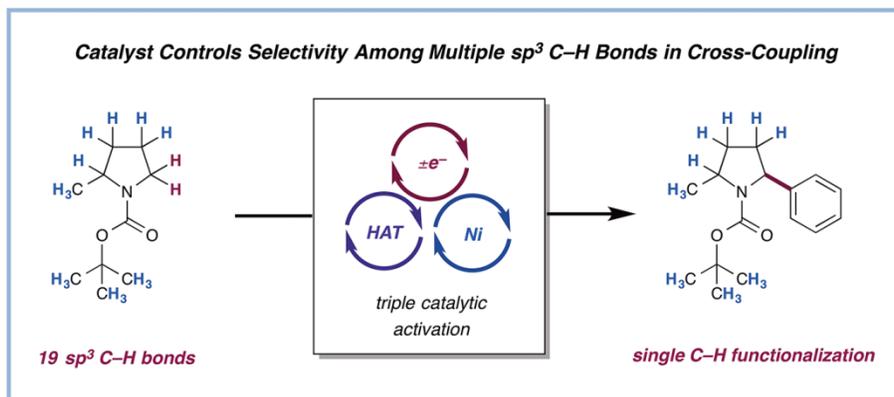
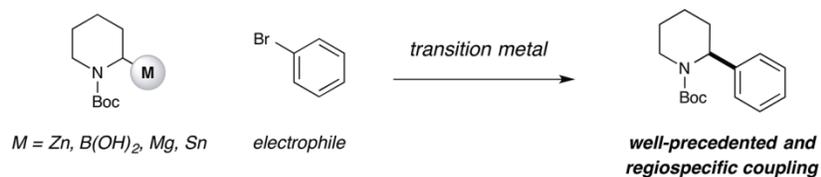


Fig. 1. Photoredox-mediated hydrogen atom transfer and nickel catalysis enable highly selective cross-coupling using sp^3 C–H bonds as latent nucleophiles.

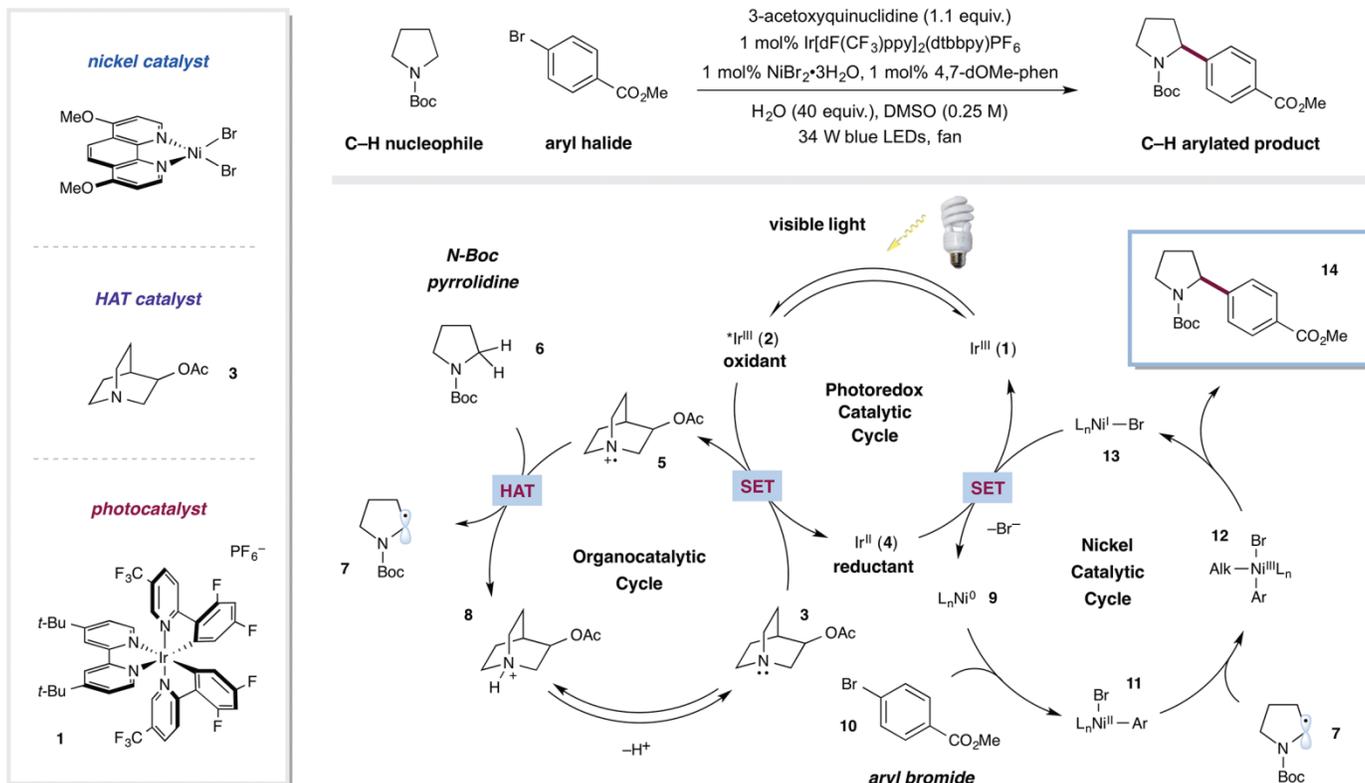
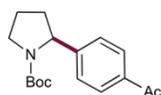
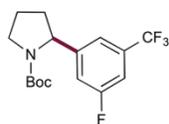


Fig. 2. Photoredox, HAT, and nickel-catalyzed cross-coupling: proposed mechanistic pathway and catalyst combination. Ac, acetyl; *t*-Bu, *tert*-butyl; Boc, *tert*-butoxycarbonyl; LED, light-emitting diode; SET, single-electron transfer; HAT, hydrogen atom transfer.

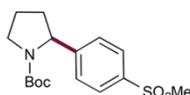
aryl bromides



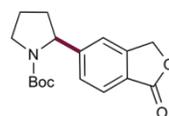
(±)-**15** 84% yield



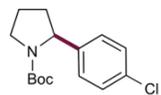
(±)-**16** 71% yield



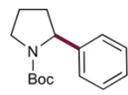
(±)-**17** 78% yield



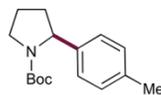
(±)-**18** 76% yield



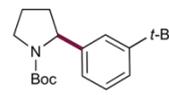
(±)-**19** 70% yield



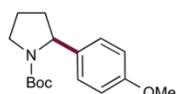
(±)-**20** 72% yield



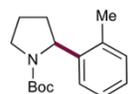
(±)-**21** 73% yield



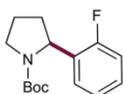
(±)-**22** 79% yield



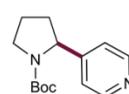
(±)-**23** 64% yield



(±)-**24** 70% yield

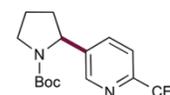


(±)-**25** 60% yield

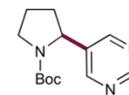


(±)-**26** 65% yield

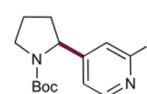
aryl chlorides



(±)-**27** 81% yield

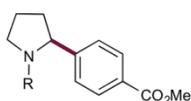


(±)-**28** 61% yield

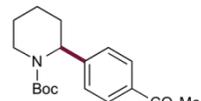


(±)-**29** 83% yield

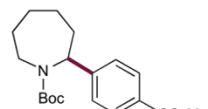
amines



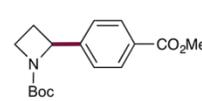
(±)-**14** R = Boc 81% yield
 (±)-**30** R = Piv 79% yield
 (±)-**31** R = Cbz 51% yield
 (±)-**32** R = Bac 80% yield*



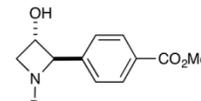
(±)-**33** 42% yield



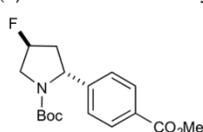
(±)-**34** 69% yield



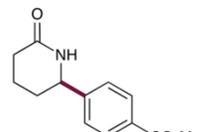
(±)-**35** 58% yield



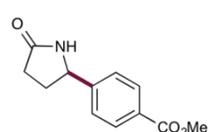
(±)-**36** 45% yield, >20:1 d.r.



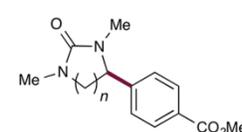
37 68% yield, 3:1 d.r.



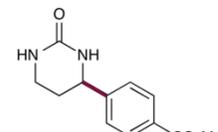
(±)-**38** 62% yield



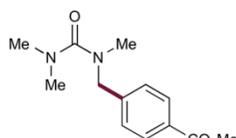
(±)-**39** 69% yield



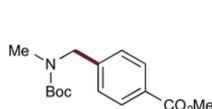
(±)-**40** n = 1 84% yield, 3:1 r.r.†
 (±)-**41** n = 2 71% yield, 1:1 r.r.†



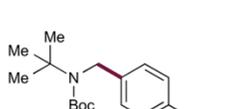
(±)-**42** 70% yield



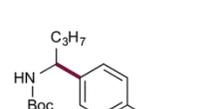
43 74% yield



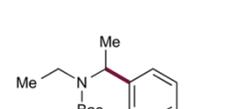
44 65% yield



45 47% yield

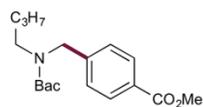


(±)-**46** 58% yield



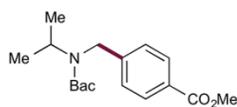
(±)-**47** 66% yield

methyl vs. methylene



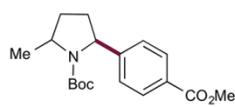
48 78% yield
 4:1 r.r.‡

methyl vs. methine



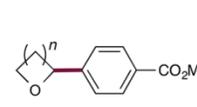
49 82% yield
 single regioisomer

methylene vs. methine



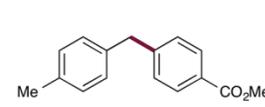
(±)-**50** 62% yield, 1:1 d.r.
 single regioisomer

ethers



(±)-**51** n = 2 76% yield
 (±)-**52** n = 1 53% yield

benzylic C-H



53 54% yield[§]

Fig. 3. Photoredox, HAT, and nickel-catalyzed cross-coupling: Aryl halide and C-H nucleophile scope. All yields are isolated yields. Reaction conditions as in Fig. 2; see Supplementary Material for experimental details. Ac, acetyl; *t*-Bu, *tert*-butyl; Boc, *tert*-butoxycarbonyl; Piv, pivalate; Cbz, benzyloxycarbonyl; Bac, *tert*-butylaminocarbonyl. *Reaction performed with 4-bromobenzotrifluoride to deliver *N*-Bac 2-(4-trifluoromethylphenyl)pyrrolidine. †Minor regioisomer is arylated on Me position. ‡Minor regioisomer is arylated on α -amino methylene position. §Yield determined by ¹H NMR.

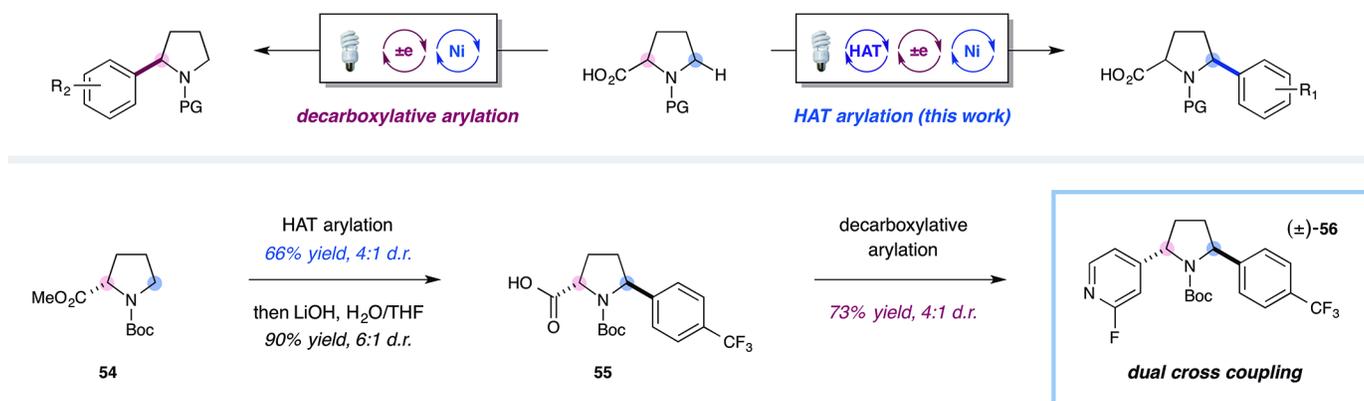


Fig. 4. Regioselective arylation: employing C–H arylation and decarboxylative arylation delivers differentially arylated pyrrolidine product. All yields are isolated yields. See Supplementary Material for experimental details.



Native functionality in triple catalytic cross-coupling: sp^3 C-H bonds as latent nucleophiles

Megan H. Shaw, Valerie W. Shurtleff, Jack A. Terrett, James D. Cuthbertson and David W. C. MacMillan (April 28, 2016)
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Editor's Summary

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